Biomedical Research and Therapy 2023, 10(5):5701-5716

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Review Article

Effects of Remdesivir and Favipiravir on Covid-19 Clinical Outcomes : A Systematic Review and Meta-Analysis

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ABSTRACT

Introduction: After nearly two years, there is still no proven treatment for infection with severe Acute Respiratory Syndrome Coronavirus-2 (SARS-CoV-2)—the virus that causes Covid-19. Currently, the two most widely known drugs for treating Covid-19 are remdesivir and favipiravir. Therefore, this study aimed to evaluate the effects of remdesivir and favipiravir on Covid-19 clinical outcomes. **Methods:** A systematic review of the literature on the PubMed and Scopus databases was undertaken to identify studies that have examined the effects of remdesivir and favipiravir on Covid-19 outcomes. To weighted group mean differences for within- and between-group comparisons, odds ratio effect sizes, and random-effects models were used. Subgroup analyses were also conducted to determine the effects of potential sources of heterogeneity, which was assessed using the I-squared (I^2) test. **Results:** Twenty-eight studies with a total of 10,871 adult participants were included in the analysis. According to pooled analysis results, there was no statistically significant difference between the remdesivir/favipiravir and control groups in terms of mortality, intensive care unit admissions, or adverse effects ($p > 0.05$). Mean hospitalization duration was significantly different for those receiving remdesivir (0.1-day increase) and favipiravir (0.06-day decrease), but these findings included significant levels of publication bias. Treatment duration was found to be a significant source of heterogeneity in the mortality results. **Conclusion:** Remdesivir and favipiravir have no effect on mortality, intensive care unit admissions, or duration of hospitalization for Covid-19 patients.

Key words: Remdesivir, Favipiravir, Covid-19, Mortality, ICU admission

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History

- Received: Mar 15, 2023
- Accepted: May 20, 2023
- Published: May 31, 2023

DOI : 10.15419/bmrat.v10i5.811

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INTRODUCTION

Severe Acute Respiratory Syndrome Coronavirus-2 (SARS-CoV-2) was first reported in late December 2019 in Wuhan, China, and has since spread globally[1]. By October 2021, more than 237 million people had been infected by the virus that causes Covid-19 and approximately 4.5 million people had died from their infections[2]. The Covid-19 pandemic is an ongoing global health crisis that requires immediate attention to quickly find an appropriate treatment to reduce global mortality and morbidity associated with the disease. Currently, drugs including arbidol[3], ribavirin[4], chloroquine or hydroxychloroquine, lopinavir/ritonavir, remdesivir, and favipiravir are among those used to treat the infection experimentally. There is no known cure for SARS-CoV-2 infection[5], although there are some effective treatments. Specifically, convalescent plasma[6], interleukin (IL)-1 or IL-6 inhibitors[7], and interferons[3] have been used as supportive therapy. Medications given to COVID-19 patients include antimalarial drugs such as chloroquine and hydroxychloroquine, which are also used to treat autoimmune diseases[8], while lopinavir/ritonavir is an FDA-approved HIV treatment drug[9]. Gilead Science collaborated with the US Centers for Disease Control and Prevention (CDC) and the US Army Medical Research Institute of Infectious Diseases to develop remdesivir, an intravenous adenosine nucleotide analog prodrug with activity against several RNA viruses[10,11]. Similarly, favipiravir is an antiviral that works against viruses containing RNA. Toyama Chemical Company was the first to approve this drug, which was used to treat influenza in Japan and China[3,12–15].

The Solidarity World Health Organization International Trial was a collaborative effort to find potential treatments for Covid-19 that involved 52 countries. Drugs that were investigated included remdesivir, hydroxychloroquine, lopinavir, and interferon, of which remdesivir, hydroxychloroquine, lopinavir, and interferon were found to be ineffective or have little effect for the treatment of Covid-19 hospitalized patients[16]. In contrast, according to the findings of another review study, there was a higher rate of improvement in patients who received remdesivir than

Cite this article : Nazari S S H, Karimi R, Mohammadian M, Maghsoudi M, Khani Y. **Effects of Remdesivir and Favipiravir on Covid-19 Clinical Outcomes : A Systematic Review and Meta-Analysis**. *Biomed. Res. Ther.;* 2023, 10(5):5701-5716.

in those who received a placebo; however, there was no difference in the 14-day mortality rate [17]. Another review found that remdesivir significantly reduced recovery time and the occurrence of side effects, but was ineffective in treating the disease if used alone. Hence, there was improved performance when remdesivir was combined with other antiviral drugs [18]. Favipiravir was found to be effective in treating patients with mild to moderate disease only [19].

Covid-19 is treated with antiviral drugs and supportive therapies, and numerous studies and clinical trials have been carried out to confirm the effectiveness of the drugs in combating infection. Therefore, this study aims to support the development and implementation of effective treatments for Covid-19 and analyze the results of published studies investigating the use of either remdesivir or favipiravir in COVID-19 patients to clarify their efficacy in relation to different patient outcomes.

METHODS

Research Design

This meta-analysis followed the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) guidelines [20,21]. A quality check was conducted using the Critical Appraisal Skills Program checklist for randomized control trials (RCTs) and cohort studies [22,23].

Search Strategy

Three authors independently searched the MEDLINE (PubMed) and Scopus databases for published articles. The search strategy was guided by the keywords "COVID-19," "remdesivir," and "favipiravir". A complete list of the keywords used for the search is presented in the appendix. Case-control, cohort, and RTCs were included in the searches. All of the articles were examined and there was no limitation according to study time or location. The population, intervention type, and study comparison criteria were adjusted to determine study inclusion and exclusion criteria.

Inclusion and Exclusion Criteria

The inclusion criteria were:

1) Studies using case-control, cohort, or RCT designs;

2) COVID-19 patients with positive laboratory tests;

3) Remdesivir and/or favipiravir having been administered to the treatment/intervention group;

4) Any medicines other than Remdesivir and Favipiravir in the control group; and

5) Disease and treatment-related outcomes were measured.

Case reports, reviews, animal research, *in silico* and *in vitro* studies, as well as articles with full texts that were unavailable (after contacting the authors), were excluded from the study.

Data Extraction and Quality Control

Two authors independently extracted data from the selected articles using a checklist. First, the titles and abstracts of identified articles were examined, and articles that were unrelated to the meta-analysis were excluded. The full texts of the remaining articles were then reviewed and included in the analysis based on the inclusion criteria. Data on the first author, year of publication, location, type of study, blinding, randomization, disease severity, sample size, type and dose of the treatment drug, population type, other treatments used, duration of treatment, age, gender, length of the follow-up period, length of the hospitalization period, recovery ratio, recovery time, mortality rate, days to first improvement, mechanical ventilation, intensive care unit (ICU) admission, ICU length of stay, acute respiratory distress syndrome, intubation, and any adverse effects in treatment and control groups were collected.

Statistical Analysis

We used a proposed estimation model [24] to justify the scale and outcome indicators (median, interquartile range (IQR), mean and standard deviation (SD)). We anticipated significant heterogeneity among the studies and, therefore, used a random effects model. To examine the heterogeneity of the effect-size estimates among the studies, the Q-statistic, its p-value, a forest plot, and I^2 were used. The Q-statistic was used to compare the observed and expected effect size dispersions across the studies, and the p-values for statistical significance are provided. The I^2 value is the ratio of real to observed heterogeneity. I^2 values between 0% and 50% were considered to be acceptable heterogeneity, while values greater than 50% were considered to indicate significant heterogeneity [25]. Subgroup analysis and meta-regression were used to determine the sources of heterogeneity when it was significant [26]. A funnel plot and Egger's regression test were used to evaluate publication bias (given the low power of the test, a = 0.1 was used) [27]. Stata Statistical Software Version 15.1. (StataCorp LP., College Station, TX, USA) was used for all analyses.

Table 1: Characteristics of included studies

No	First author	Country	Study Design	Blinding type	Randomization	Covid status	Sample Size	Population type	Treatment protocol (days and dose)	Mean Age	Follow-up Duration (days)	Control group	Outcomes
1	Alessandro Russo[28]	Italy	Observentional Cohort	No data	No data	Hospitalization	294	Normal	Remidisivir	63.20	30	non	-Hospitalization Days -Mortality
2	Andreas Barratt-Due[29]	Norway	Interventional	Triple	yes	Hospitalization	42	Normal	Remidisivir 100 mgper day	59.70	90	routine cares	-Mortality
3	Anıl Uc[30]	Turkey	Observentional Cohort	No data	Yes +	Hospitalization	48	Normal	Favipiravir Hydro 1200 mg per day	58.50	14	Hydrox	-Mortality -ICU admition
4	Areej A Malhani[31]	Saudi Arabia	Observentional Cohort	No	No	Hospitalization	154	Normal	Favipiravir 1600 mg per day	55	28	IFN	-Hospitalization Days -Mortality -ICU admition
5	Carlos K H Wong[32]	Hong Kong	Observentional Cohort	No	No	Hospitalization	466	Normal	Remid+Dexametasone	64.80	11	Dexa	-Mortality
6	Christoph D. Spinner[33]	United States, Europe, and Asia	Interventional	No	Yes	Hospitalization	193	Normal	Remidisivir 100 mgper day	55.66	11	routine cares	-Mortality -Adverse effect -
7	Eun-Jeong Joo[34]	S. Korea	Observentional Cohort	No	No	Hospitalization	48	Normal	Remidisivir 100 mg per day	69.02	30	routine cares	Hospitalization Days -Time to recovery -Mortality

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Table 1 continued

No	First author	Country	Study Design	Blinding type	Randomization	Covid status	Sample Size	Population type	Treatment protocol (days and dose)	Mean Age	Follow-up Duration (days)	Control group	Outcomes
8	Faryal Khamis[35]	Oman	Interventional	No	Yes	Hospitalization	44	Normal	Favipiravir 1600 mg per day	54	14	Routine cares	-Hospitalization Days -Mortality -ICU admition
9	George A Diaz[36]	USA	Observentional Cohort	No	No	Hospitalization	286	Normal	Remidisivir 100 mg per day	61.40	30	Routine cares	-Mortality
10	Halit ÇINARKA[37]	Turkey	Observentional Cohort	No data	No data	Hospitalization	131	Normal	Favipiravir	55.97	14	lopinavir	-Hospitalization Days -Mortality -ICU admition
11	Hany M Dabbous[38]	Egypt	Interventional	No data	Yes	Hospitalization	44	Normal	Favipiravir 1200 mg per day	34.86	10	chloroquin	-Heospitalization Days -Mortality
12	Havva Kocayiğit[39]	Turkey	Observentional Cohort	No	No data	ICU	65	Normal	Favipiravir	69.80	70	lopinavir	-Mortality -ICU stay

Continued on next page

Table 1 continued

No	First author	Country	Study Design	Blinding type	Randomization	Covid status	Sample Size	Population type	Treatment protocol (days and dose)	Mean Age	Follow-up Duration (days)	Control group	Outcomes
13	J.H. Beigel[40]	United States (45 sites), Denmark (8), the United Kingdom (5), Greece (4), Germany (3), Korea (2), Mexico (2), Spain (2), Japan (1), and Singapore (1).	Interventional	Double	Yes	Hospitalization	541	Normal	Remidisivir 100 mg per day	58.60	10	placebo	-Time to recovery -Mortality -Adverse effect
14	Lakshmi Mahajan[41]	India	Interventional	No	Yes	Hospitalization	34	Normal	Remidisivir 100 mg per day	58.08	12	routine cares	-Mortality
15	Markos Kalligeros[42]	USA	Observentional Cohort	No	No	Hospitalization	99	Normal	Remidisivir 100 mg per day	58.66	28	routine cares	-Mortality
16	Masaharu Shinkai[43]	Japan	Interventional	Single	Yes	No data	107	Normal	Favipiravir 1600 mg per day	43.80	28	placebo	-Mortality -Adverse effect
17	Masoud Solaymani-Dodaran[44]	Iran	Interventional	Single	Yes	Hospitalization	190	Normal	Favipiravir 1800 mg per day	58.60	10	lopinavir	-Mortality -ICU admition
18	Michael E Ohl[45]	USA	Observentional Cohort	No data	No data	Hospitalization	1172	Normal	Remidisivir	66.60	30	Routine cares	-Mortality -ICU admition
19	Nouf K Almaghlouth[46]	USA	Observentional Cohort	No	No	Hospitalizatic	33	Normal	Remid+Tocilizum 100 mg per day		7	tocli	-Mortality

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Table 1 continued

No	First author	Country	Study Design	Blinding type	Randomization	Covid status	Sample Size	Population type	Treatment protocol (days and dose)	Mean Age	Follow-up Duration (Days)	Control group	Outcomes
20	Regine Padilla [47]	USA	Observentional Cohort	No	No	Hospitalization	11	Normal	Remidisivir 100 mgper day		7	Convalescent plasma	Mortality
21	Robert Flisiak [48]	Poland	Observentional Cohort	No	No	Hospitalization	122	Normal	Remidisivir 100 mg per day	58.70	28	lopinavir	-Hospitalization Days -Mortality -Adverse effect
22	Susan A Olender [49]	USA	Observentional Cohort	No	No	Hospitalization	298	Normal	Remidisivir 100 mg per day		14	routine cares	-Time to recovery -Mortality
23	Toshiki Kuno [50]	Japan, USA	Observentional Cohort	No	No	Hospitalizatic	1336	Normal	Remidisivir 100 mg per day	65.70	14	steroids	-Mortality -ICU admition
24	Vishal Gupta [51]	India	Observentional Cohort	No data	No	Hospitalization	414	Normal	Remidisivir	57	14	tocli	-Hospitalization Days -Mortality
25	WHO Solidarity Trial Consortium; Hongchao Pan [52]	WHO	Interventional	Double	Yes	Hospitalization	2743	Normal	Remidisivir 100 mg per day		30	placebo	-Mortality

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Table 1 continued

No	First author	Country	Study Design	Blinding type	Randomization	Covid status	Sample Size	Population type	Treatment protocol (days and dose)	Mean Age	Follow-up Duration (days)	Control group	Outcomes
26	Yeming Wang[53]	Italy	Interventional	Double	Yes	Hospitalization	158	Normal	Remidisivir 200 mg per day	64	28	pelacebo	-Hospitalization Days -Time to recovery -Mortality
27	Zainab Almoosa[54]	Saudi Arabia	Observentional Cohort	No data	no data	Hospitalizatic	110	Normal	Favipiravir 1400 mg per day	56.80	14	routine cares	-Time to recovery -Mortality -ICU admition
28	Zeno Pasquini[55]	Italy	Observentional Cohort	No data	no data	ICU	25	Normal	Remidisivir 100 mg per day	64	10	ventilation	-Mortality

Abbreviation: **ICU**: Intensive care unit

RESULTS

Systematic Search and Characteristics of the Included Studies

The initial search uncovered 8,329 relevant records of which 3,561 duplicates were removed. After screening the titles and abstracts, 633 studies were considered eligible for further screening. Next, the full texts of the studies were assessed and 28 studies with a total of 10,871 adult participants were found to be eligible for inclusion in the meta-analysis (**Figure 1**).

Pooled Analysis of Covid-19 Outcomes After Receiving Remdesivir or Favipiravir

As the included studies reported their outcomes differently, event counts rather than percentages and proportions were used. For mortality rates, some studies used counts while others used ORs. Therefore, an analysis was conducted for both indicators after converting the counts into ORs and 95% CIs. Hospitalization duration was also measured using the mean indicator and is presented as mean differences.

Mortality Rate

According to the results of a pooled analysis of 17 studies, there was no statistically significant difference in the mortality rate between the remdesivir and control groups (p: 0.493). Similarly, based on the results of a pooled analysis of 8 studies, there was no significant difference in the mortality rate between the favipiravir and control groups (p: 0.774). Heterogeneity was high (> 50%) for all of the studies; although, no publication bias was observed (Egger's test p-value > 0.20) (**Table 2**, **Figures 2 and 3**).

Admission to the ICU

Results from a pooled analysis of 3 studies using remdesivir and 4 studies using favipiravir[30,31,37,44,45,47,50,54] found no statistically significant differences in ICU admission outcomes between the intervention and control groups (p-value for remdesivir: 0.785, p-value for favipiravir: 0.483). The heterogeneity was high (> 50%) and significant, but no publication bias was found (**Table 2**, **Figures 4 and 5**).

Adverse Effects

A pooled analysis of 4 studies[33,40,48] indicated that patients receiving remdesivir had no significantly higher adverse effects compared to control groups (p: 0.732). While the heterogeneity was both high (> 50%) and significant, no publication bias was found. This analysis was not possible for favipiravir due to the low number of available, published studies (< 3) (**Table 2**,**Figures 5 and 6**).

Hospitalization Duration

The pooled analysis for hospitalization duration consisted of 3 studies[34,35,48], which showed that the use of remdesivir significantly increased hospitalization duration in the intervention groups by 0.1 days (p: 0.000). In contrast, the results of an analysis of 3 studies[31,37,38] that used favipiravir showed significantly reduced hospitalization duration (by 0.06 days compared to the control groups (p: 0.019)). However, high heterogeneity (> 50%) and publication bias were observed (**Table 2**, **Figures 8 and 9**).

The mortality rate in different subgroups was not significantly different between the intervention and control groups (**Table 3**). The subgroups analyzed in this meta-analysis included study design, treatment duration (median: 7 days), and age (median: 59 years). Analyzing other outcomes was not possible due to the lack of studies reporting on each possible subgroup variable.

Table 4 presents the possible sources of the high heterogeneity observed in the analysis. The only variable that significantly effected heterogeneity was treatment duration, which was significant for both remdesivir and favipiravir. Further analysis was not possible for the other outcomes due to the lack of published studies reporting on the different subgroup variables.

DISCUSSION

This study aimed to evaluate the effectiveness of two well-known drugs, remdesivir and favipiravir, for treating Covid-19 infection. Remdesivir was introduced as an effective drug for the treatment of Covid-19 after obtaining its first emergency use authorization in May 2020 in the United States and then later in Japan. However, its use has had many critics[56]. Unfortunately, despite both the passage of time and an increase in the number of observational studies and RCTs, questions regarding the efficacy of these drugs remain unanswered primarily because the results have been controversial and heterogeneous between the various investigations. One way to address this issue is to conduct systematic reviews and meta-analysis studies.

As a ribonucleotide analog and selective inhibitor of the viral RNA polymerase enzyme, favipiravir performs a wide range of antiviral activities against RNA-carrying viruses, which includes blocking viral genome replication and transcription. In Japan and China, favipiravir is licensed for the treatment

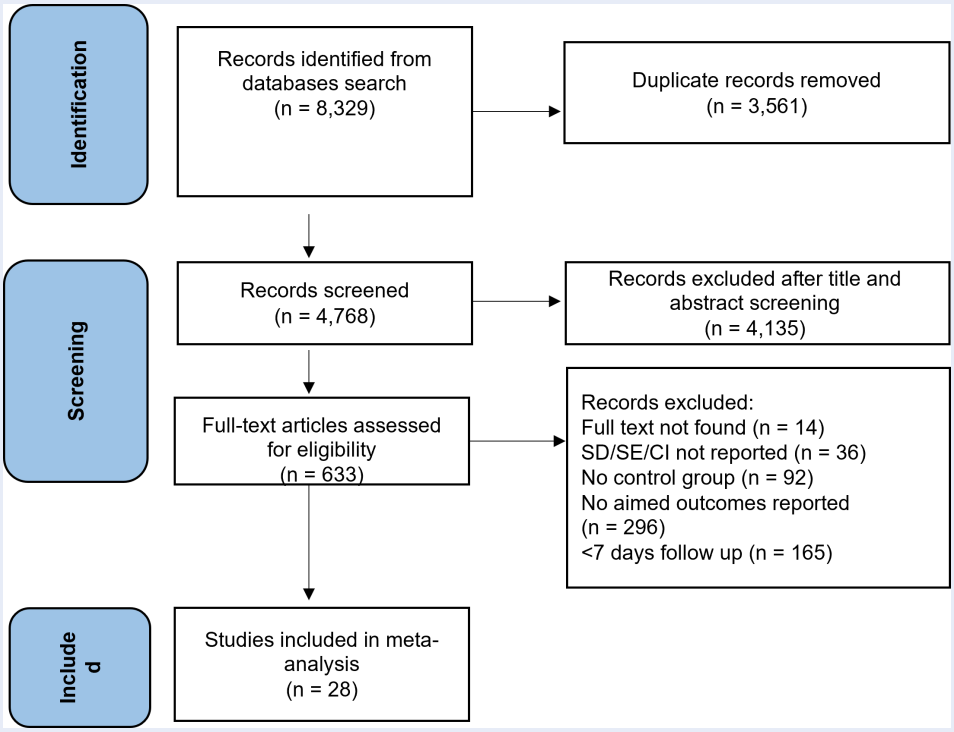

Figure 1: **PRISMA flow diagram of search and included studies.**

Table 2: Effect of Remdesivir and Favipiravir between intervention and control groups

Outcome	N studies	OR (95% CI)	Heterogeneity $\%I^2$ (p-value)	Egger's test p-value
Mortality[1]				
Remdesivir	17	0.893 (0.676-1.180)	78.47 (0.003)	0.654
Favipiravir	8	0.984 (0.540-1.793)	54.65 (0.038)	
ICU admission				
Remdesivir	3	0.74 (0.26-1.86)	97.09 (0.001)	0.772
Favipiravir	4	0.49 (0.11-2.09)	91.44 (0.001)	
Any adverse effects				
Remdesivir	4	0.86 (0.46-1.58)	90.06 (0.002)	0.583
Outcome	**N studies**	**Mean difference p-value**	**Heterogeneity $\%I^2$ (p-value)**	**Egger's test p-value**
Hospitalization Duration, days				
Remdesivir	3	0.000	96.15 (0.000)	0.017
Favipiravir	3	0.019	77.54 (0.030)	

[1]: Using reported counts and ORs to calculate pooled-OR and 95%CI
*: Statistically significant ($p < 0.05$)

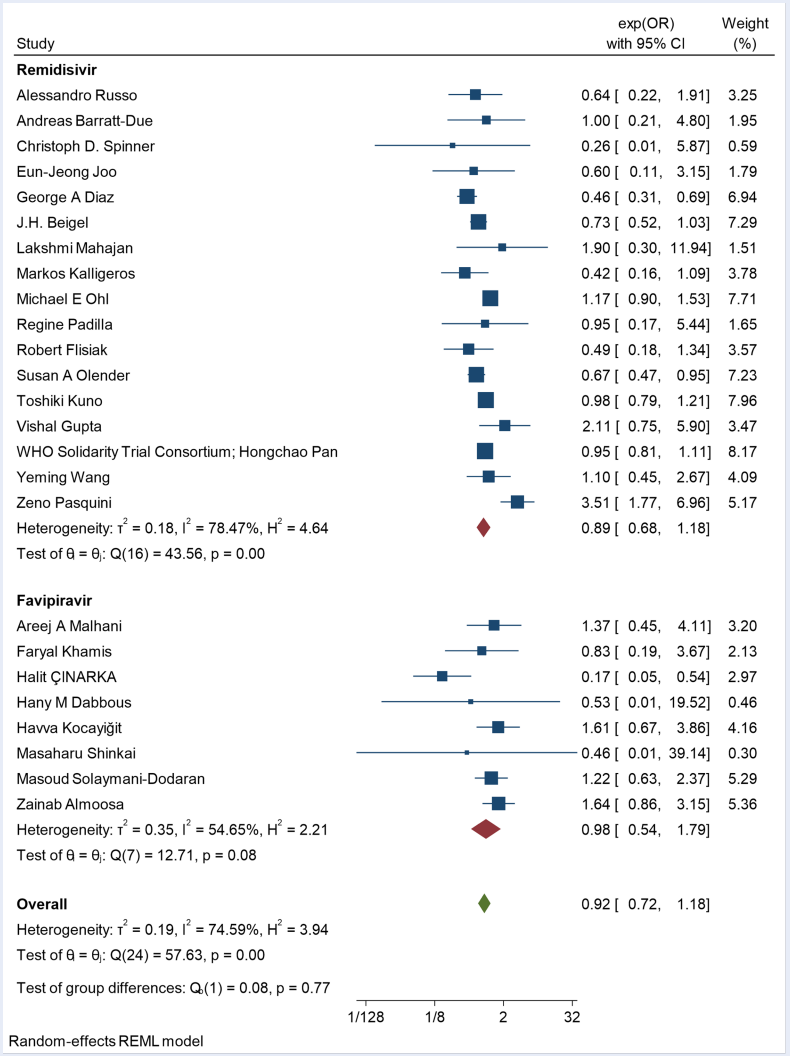

Figure 2: **Effect size of interventions on mortality (OR), forest plot.**

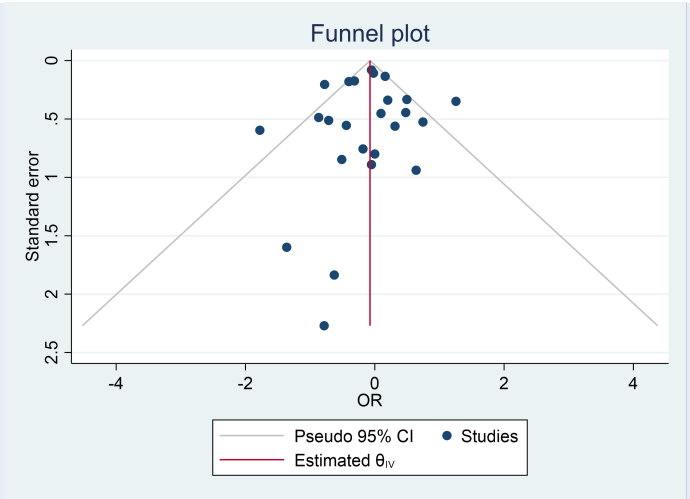

Figure 3: **Funnel plot for mortality studies.**

Table 3: Subgroup analysis of effect of Remdesivir and Favipiravir between intervention and control groups

Outcome	Remdesivir effect p-value/%I^2	Favipiravir effect p-value/%I^2	N studies
Mortality/Study design			
Interventional	0.418 / 18.90	0.632 / 0.00	11
Observational	0.325 / 28.24	0.125 / 79.20	14
Treatment Duration			
<7	0.652 / 0.00	0.238 / 28.15	10
>7	0.896 / 0.00	0.623 / 0.00	10
Mean Age			
<59	0.119 / 62.82	0.156 / 42.12	13
>59	0.965 / 64.23	0.178 / 44.27	10

Table 4: Meta regression of possible sources of heterogeneity

Outcome	Remdesivir p-value (%I^2)	Favipiravir p-value (%I^2)
Mortality		
Study design	0.835 (63.5)	0.089 (19.2)
Hospitalization section	0.864 (64.24)	-
Treatment Duration	0.049 (0.00)	0.010 (0.00)
Mean Age	0.510 (62.82)	0.473 (41.17)
Country (continent)	0.711 (63.11)	0.654 (33.12)

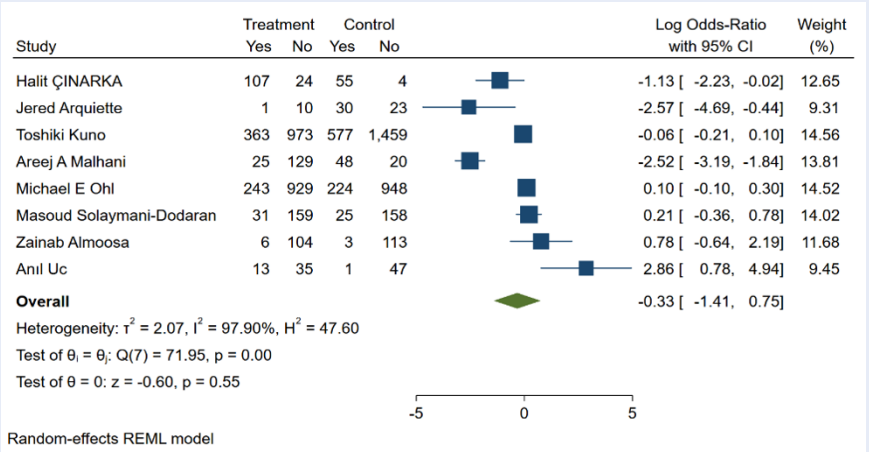

Figure 4: Effect size of interventions on intensive care unit admission (log OR), forest plot.

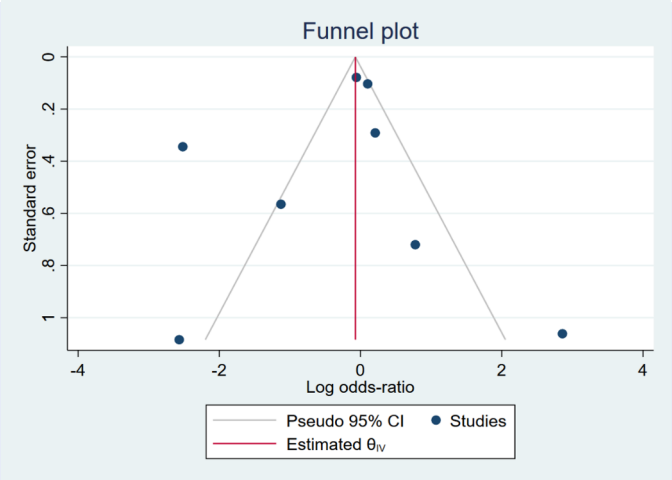

Figure 5: **Funnel plot for intensive care unit admission studies.**

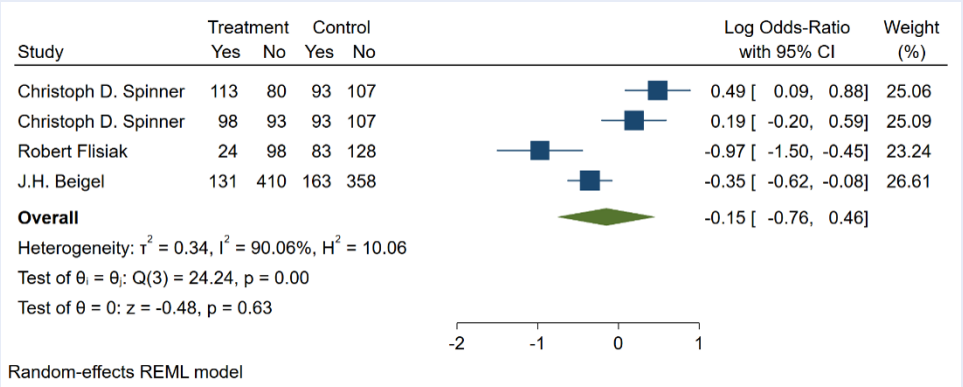

Figure 6: **Effect size of interventions on adverse effects (log OR), forest plot.**

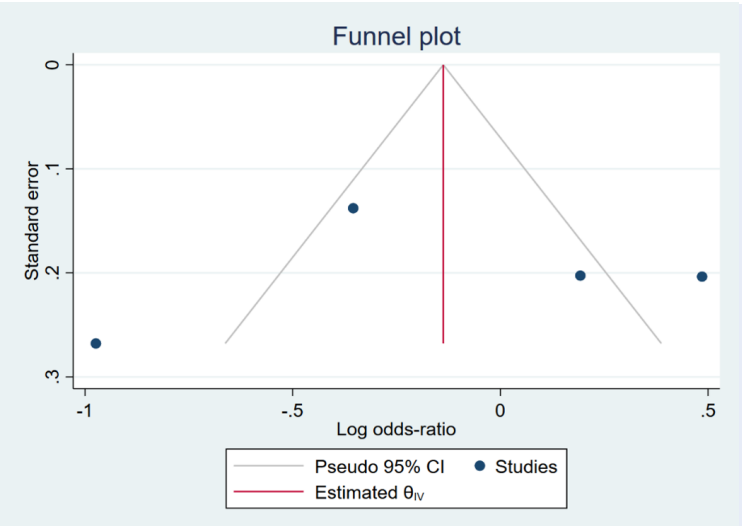

Figure 7: **Funnel plot for adverse effects studies.**

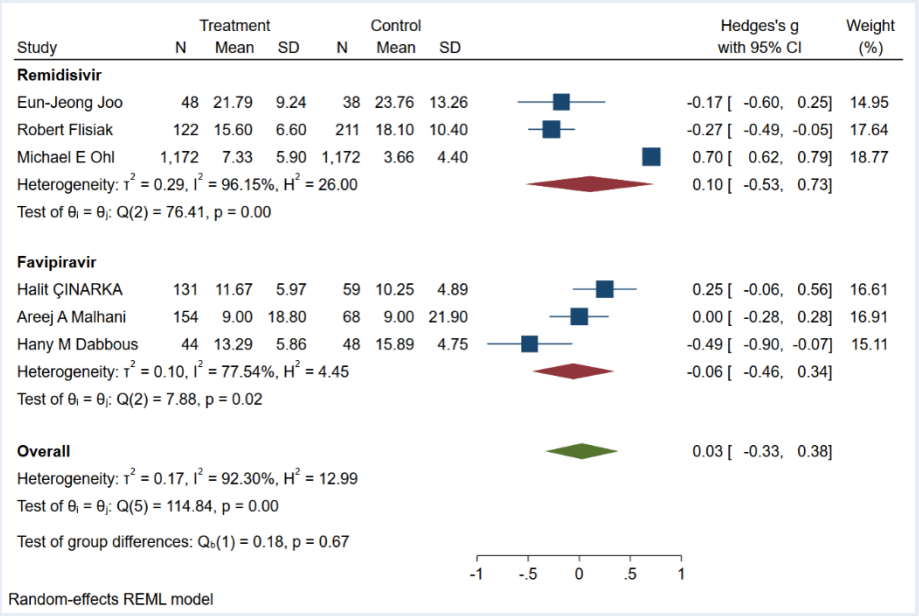

Figure 8: **Effect size of interventions on hospitalization duration, forest plot.**

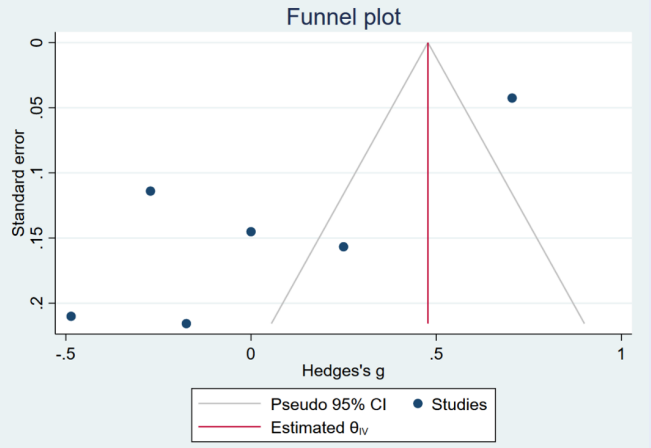

Figure 9: **Funnel plot for hospitalization duration studies.**

of novel influenza viruses. It is also effective against Ebola and other RNA-based viruses that cause hemorrhagic fevers[35]. However, according to the findings of the current meta-analysis, favipiravir had no significant effect on reducing the mortality rate or ICU admissions in Covid-19 patients. Other meta-analyses have also found that the drug does not decrease many of the indicators associated with Covid-19, including death, hospitalization duration, transfer to the ICU, *etc.*[57,58]. However, in this study, favipiravir was found to reduce hospitalization duration by 0.06 days. Although this reduction was statistically significant, it is clinically equivalent to approximately 86 minutes, which would not be considered important from a patient perspective. We also found that favipiravir administration did not induce more side effects compared with controls. This result is consistent with those from another meta-analysis[59]. However, few interventional and secondary studies using favipiravir have been conducted, and finding high-quality interventional studies with large sample sizes is challenging. Furthermore, the high heterogeneity in the results suggests substantial variation in the target parameters of these studies.

Remdesivir is an adenosine nucleotide analogue prodrug that inhibits viral replication by inducing chain termination in the RNA-dependent RNA polymerase enzyme of SARS-CoV-2[60]. However, there are debates concerning the effectiveness of remdesivir, and studies, including meta-analyses, have not yet reached

a consensus regarding its efficacy. According to some of the articles used in the current study, the use of remdesivir did not effect the mortality or ICU admission rates in Covid-19 patients. In contrast, others have found that the use of the drug reduced the mortality rate by 34% (OR: 0.66). These inconsistent results have been found in other meta-analyses as well[61–63]. We also found that taking remdesivir increased treatment duration by 0.1 days (144 minutes). While this finding is not consistent with other, similar studies that have found remdesivir neither changes hospitalization duration[61] nor reduces it[62,63], it should be noted that there was both high heterogeneity and publication bias, both of which could have affected our findings. The effect of the treatment duration variable in heterogeneity should be also taken into account. Specifically, if only this variable is considered, it is possible to assume that treatment duration changes remdesivir's efficacy.

One limitation of this study (and similar meta-analyses) is the severe lack of high-quality, interventional studies with appropriate sample sizes, sufficient follow-up periods, and similar treatment protocols needed to reduce heterogeneity. One of the strengths of this study was the simultaneous review of observational and interventional studies as well as sub-group analyses of different outcome variables.

CONCLUSION

Based on the results of this meta-analysis, both remdesivir and favipiravir have very slight or no effect on mortality rates, ICU admissions, or hospitalization duration in Covid-19 patients. However, more vigorous interventional studies are needed before coming to firm conclusions about the effects of these drugs on covid-19 patient outcomes.

ABBREVIATIONS

FDA: United States of America Food and Drug Administration; **PRISMA**: The Preferred Reporting Items for Systematic Reviews and Meta-Analysis; **ICUs**: Intensive care units; **ARDS**: Acute respiratory distress syndrome; **IQR**: Interquartile range; **SD**: Standard Deviation

ACKNOWLEDGMENTS

None.

AUTHOR'S CONTRIBUTIONS

Y.KH: Contribution to study concept and design, acquisition, analysis and interpretation of data, drafting of the manuscript. M.M: Contribution to study concept and design, drafting of the manuscript. R.K: Contribution to study concept and design, drafting of the manuscript SS. HN: Contribution to study concept and design, acquisition, analysis and interpretation of data, drafting of the manuscript. All authors read and approved the final manuscript.

FUNDING

None.

AVAILABILITY OF DATA AND MATERIALS

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

All methods were carried out in accordance with relevant guidelines and regulations.

CONSENT FOR PUBLICATION

Not applicable.

COMPETING INTERESTS

The authors declare that they have no competing interests.

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